ACE-inhibitor use and the long-term risk of renal failure in diabetes

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The incidence of end-stage renal disease (ESRD) owing to diabetes has continued to increase despite the extensive use of angiotensin-converting enzyme (ACE) inhibitors to prevent diabetic nephropathy, primarily from evidence of short-term effectiveness. We assessed the long-term effect of ACE inhibitors on the risk of ESRD. We formed a population-based cohort of all diabetic patients treated with antihypertensive drugs in the Province of Saskatchewan, Canada, between 1982 and 1986. The patients were followed up to the end of 1997 to identify cases of end-stage renal failure. A nested case–control analysis was used with the controls matched to each case on age, diabetes type, and duration of follow-up. The cohort comprised 6102 subjects, of which the 102 cases who developed end-stage renal failure were matched to 4129 controls. Relative to thiazide diuretic use, the adjusted rate ratio of end-stage renal failure associated with the use of ACE inhibitors was 2.5 (95% confidence interval 1.3–4.7), whereas it was 0.8 (95% confidence interval 0.5–1.4) for beta-blockers and 0.7 (95% confidence interval 0.4–1.3) for calcium antagonists. The rate ratio of end-stage renal failure with the use of ACE inhibitors was 0.8 (95% confidence interval 0.3–2.5) during the first 3 years of follow-up, but increased to 4.2 (95% confidence interval 2.0–9.0) after 3 years. ACE-inhibitor use does not appear to decrease the long-term risk of end-stage renal failure in diabetes. Our data suggest instead that ACE inhibitors might actually increase this risk, which may possibly contribute to the continued increasing incidence of ESRD owing to diabetes.

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Angiotensin-converting enzyme (ACE) inhibitors have been used for an increasing number of indications since their introduction as antihypertensive drug therapy for treatment-resistant hypertension.[1–6] One of these suggested indications, namely slowing the rate of progression of nephropathy in diabetic patients with or without hypertension,[3] can potentially have a major impact on this disease. Indeed, diabetic nephropathy, occurring in 20–40% of diabetics, is currently believed to be the most important cause of morbidity and mortality among diabetic patients.[7] As diabetic nephropathy accounts for nearly 45% of new patients reaching end-stage renal disease (ESRD) in the USA, the clinical impact of potential ACE-inhibitor-mediated renal effects, beyond that resulting from blood pressure reduction, should be substantial.[8] However, despite the extensive use of ACE inhibitors to prevent diabetic nephropathy, the incidence of ESRD owing to diabetes in the USA has increased 266% in the decade between 1984 and 1994.[9] Although increasing incidence of diabetes, longer survival, and liberalized acceptance criteria of ESRD programs may account for a part of it, other possible explanations should be entertained.[10]

The evidence for the effectiveness of ACE inhibitors in preventing diabetic nephropathy is surprisingly not persuasive. Although numerous studies have been conducted on the renal effects of ACE inhibitors, including a meta-analysis of more than a hundred studies that suggested that ACE inhibitors were unique in decreasing proteinuria, beyond that mediated by their hypotensive effect, and had a favorable effect on decline in glomerular filtration rate,[11] studies based on major outcomes are not all as decisive. In type I diabetes, the ACE inhibitor captopril was shown to reduce the 3-year rate of progression to dialysis, renal transplantation, or death, as well as doubling of serum creatinine, in patients with existing diabetic nephropathy and serum creatinines exceeding 1.5 mg/dl at study entry.[12] On the other hand, in a trial of hypertensive patients with type II diabetes with no nephropathy, the United Kingdom Prospective Diabetes study showed that patients on captopril had similar rates of renal failure to patients on atenolol, a beta-blocker, after more than 8 years follow-up.[13] The MIcroalbuminuria, Cardiovascular,

and Renal Outcomes (MICRO)-Heart Outcomes Prevention Evaluation study found no reduction in the rate of dialysis, a secondary outcome, in patients predominantly with type II diabetes given the ACE inhibitor ramipril after 4.5 years of follow-up.[14] Two recent randomized trials assessing the effectiveness of angiotensin-receptor blockers in patients with type II diabetes and pre-existing kidney disease found slightly lower rates of ESRD relative to placebo over 4 years.[15,16] The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial study, which includes 36% of patients with type II diabetes showed no difference in the rate of decline of glomerular filtration rate or rate of development of ESRD between the ACE inhibitor lisinopril and the diuretic chlorthalidone after 6 years of follow-up. No separate analysis for diabetic patients is given.[17] Thus, no study has yet evaluated the long-term renal effects of ACE inhibitors in type I diabetic patients and the only study that did so in type II diabetics (United Kingdom Prospective Diabetes Study), a trial of tight blood pressure control that does not represent the typical clinical experience, found no benefit.

In this population-based cohort study, we assess the long-term effect of ACE-inhibitor use on the incidence of end-stage renal failure in a large cohort of hypertensive diabetic patients.

RESULTS

The cohort consisted of 6102 diabetic patients who were dispensed an antihypertensive drug between 1982 and 1986, after excluding 37 subjects who had been hospitalized for renal disease before cohort entry. At cohort entry, the mean age was 66 years, 55% were male and 40% were first-time users of antihypertensive drugs. At cohort entry, the mean duration of diabetes was around 6 years and 44% of the cohort subjects entered the cohort treated exclusively with oral hypoglycemic agents.

During cohort follow-up, that averaged 7.8 years, 133 subjects required some dialysis treatment, of which 102 satisfied our criteria for end-stage renal failure. The corresponding rate of ESRD was 2.13 per 1000 per year and the time from cohort entry to the onset of renal failure was 5 years, ranging from 3 days to 13.5 years. Entry into the cohort was gradual over time with 16.7% entering the cohort in 1982 up to 26.5% in 1986. Half of the cases occurred during 1987–1991, whereas around a quarter of them occurred during each of 1982–1986 and 1992–1997.

All 4129 cohort members who could be matched to the cases were identified. Characteristics of the cases and their matched controls, both around 57 years of age, are presented in Table 1. The cases included more males and most used insulin. The median duration of diabetes was over 16 years. Thus, the mean time from the start of treated diabetes to outcome requiring dialysis was over 21 years for the cases. Although they were rather comparable with respect to cardiovascular disease before cohort entry, cases were much more likely to have had developed heart failure during follow-up.

Table 1 | Characteristics of cases and controls

	Cases	Controls
Number	102	4129
Age at index date[a] (years; mean ± s.d.)	56.6 ± 15.7	57.2 ± 2.4
Sex (% male)	61.8	51.4
Time from cohort entry to index date[a] (years; mean ± s.d.)	4.9 ± 3.4	4.9 ± 0.5
Diabetes treatment before index date[a] (%)		
Insulin only	45.1	45.1
Oral hypoglycemics only	13.7	13.7
Insulin and oral hypoglycemics	41.2	41.2
Median duration of diabetes before index date[a] (years)	16.6	16.5
Cardiovascular disease (%)		
Before cohort entry	11.8	15.4
Between cohort entry and index date	30.4	24.8
Congestive heart failure before index date (%)		
Before cohort entry	12.8	9.0
Between cohort entry and index date	36.3	14.4
Hypertensive drug use before cohort entry (%)	51.0	48.4

[a]Matching factors.

Table 2 displays the rate ratio of renal failure for the various classes of antihypertensive drugs dispensed during the first 90 days of follow-up. The adjusted rate ratio of ACE-inhibitor use, relative to thiazide diuretic use, is 2.5 (95% confidence interval 1.3–4.7). On the other hand, beta-blockers and calcium antagonists are not associated with renal failure risk.

Table 3 presents the rate ratio of renal failure for ACE-inhibitor use as a function of the duration of follow-up. During the first 3 years of follow-up, the adjusted rate ratio is 0.8 (95% confidence interval 0.3–2.5). However, the rate ratio after 3 years of follow-up is 4.2 (95% confidence interval 2.0–9.0). Among subjects with over 3 years of follow-up, Table 4 shows that the continuance of ACE-inhibitor use during both the first 3 years of follow-up and thereafter is associated with a rate ratio of renal failure of 7.5 (95% confidence interval 2.8–20.1), whereas for the use of ACE inhibitors only during the first 3 years, the rate ratio was 2.3 (95% confidence interval 0.3–17.5). On the other hand, ACE-inhibitor use initiated after 3 years of hypertension is associated with a rate ratio of 4.9 (95% confidence interval 2.4–9.8).

Table 5 indicates that the rate ratio of renal failure associated with ACE-inhibitor use is consistent across patients with or without heart failure before the index date, as well as patients who entered the cohort before or after December 31, 1985. It appears, however, that patients with type II diabetes (treated with oral hypoglycemics with or without insulin) have a higher rate ratio for ACE-inhibitor use than patients with type I diabetes (treated exclusively with insulin), although the two rate ratios are not significantly different ($P = 0.08$).

Table 2 | Crude and adjusted rate ratio of renal failure for ACE inhibitors and other antihypertensive drugs used during the first 90 days of follow-up

Antihypertensive drug dispensed during the first 90 days of follow-up[a]	Cases (*n*=102) %	Controls (*n*=4129) %	Matched[b] crude rate ratio	Adjusted[c] Rate ratio	Adjusted[c] 95% CI
Thiazide diuretics	45.1	51.0	1.0	1.0	Reference
ACE inhibitors:	20.6	7.8	2.9	2.5	1.3–4.7
Beta-blockers	18.6	27.8	0.8	0.8	0.5–1.4
Calcium antagonists	11.8	16.8	0.8	0.7	0.4–1.3

ACE=angiotensin-converting enzyme; CI=confidence interval.
[a]More than one agent, including other antihypertensive drugs and loop-diuretics, could have been dispensed.
[b]Matched on age, type of diabetes treatment (insulin only, oral hypoglycemics only, or combined therapy), and duration of treated diabetes.
[c]Adjusted, in addition to the matching factors, for one another, sex, continuous age, year of cohort entry, concurrent use of other antihypertensive drugs and loop-diuretics, and cardiovascular disease and congestive heart failure, both before cohort entry and during follow-up.

Table 3 | Crude and adjusted rate ratio of renal failure for ACE inhibitor use during the first 90 days of follow-up as a function of follow-up time

	Cases		Controls			Adjusted[a]	
Duration of follow-up (years)	Number	Percent users	Number	Percent users	Crude rate ratio	Rate ratio	95% CI
<3	36	16.7	1511	11.0	1.1	0.8	0.3–2.5
3–6	31	32.3	1182	9.0	5.0	4.5	1.6–12.9
>6	35	14.3	1436	3.6	3.8	3.6	1.1–11.9

ACE=angiotensin-converting enzyme; CI=confidence interval.
[a]Adjusted, in addition to the matching factors, for concurrent use of other antihypertensive drugs and loop-diuretics, sex, continuous age, year of cohort entry, and cardiovascular disease and congestive heart failure, both before cohort entry and during follow-up.

Table 4 | Crude and adjusted rate ratio of renal failure for continuance of ACE inhibitor drug use during follow-up among subjects with over 3 years of follow-up

	Cases	Controls	Crude rate ratio	Adjusted[a] Rate ratio	Adjusted[a] 95% CI
Number of subjects	66	2618			
ACE inhibitor use during follow-up among subjects with over 3 years of follow-up					
First 3 years and after 3 years	19.7	4.1	8.0	7.5	2.8–20.1
First 3 years but not thereafter	3.0	2.0	2.6	2.3	0.3–17.5
Started use after 3 years only	48.5	21.1	5.1	4.9	2.4–9.8

ACE=angiotensin-converting enzyme; CI=confidence interval.
[a]Adjusted, in addition to the matching factors, for concurrent use of other antihypertensive drugs and loop-diuretics, sex, continuous age, year of cohort entry, and cardiovascular disease and congestive heart failure, both before cohort entry and during follow-up.

Table 5 | Adjusted rate ratio of renal failure for ACE inhibitor use during the first 90 days of follow-up as a function of heart failure, year of cohort entry, and treatment of diabetes

	Cases		Controls		Adjusted[a]	
Stratum	Number	Percent users	Number	Percent users	Rate ratio	95% CI
Heart failure before cohort entry						
No	61	21.3	3144	7.7	2.7	1.3–8.2
Yes	41	19.5	985	8.6	2.2	0.5–4.7
Year of cohort entry						
1982–1985	75	10.7	3154	3.9	2.1	1.0–9.6
1986	27	48.2	975	18.9	2.8	0.7–4.9
Diabetes type (treatment) before index date						
Type I (insulin only)	46	19.6	892	10.3	1.4	0.5–3.7
Type II (oral hypoglycemics with or without insulin)	56	21.4	3237	5.8	4.1	1.8–9.2

ACE=angiotensin-converting enzyme; CI=confidence interval.
[a]Adjusted, in addition to the matching factors, for concurrent use of other antihypertensive drugs and loop-diuretics, sex, continuous age, year of cohort entry, and cardiovascular disease and congestive heart failure, both before cohort entry and during follow-up. For each stratified model, however, the stratification variable is not used as an adjustment factor.

DISCUSSION

We found that the use of ACE inhibitors by patients with diabetes is not associated with a long-term decreased risk of renal failure. Our findings suggest instead a higher risk of renal failure in those who took ACE inhibitors, even when we controlled for other risk factors.

Our findings may appear at first glance to contradict several studies on this question. The large meta-analysis,[11] which summarized the evidence from more than a hundred studies on the issue, showed that ACE inhibitors decreased proteinuria beyond that mediated by their hypotensive effect, and had a favorable effect on glomerular filtration rate. However, this effect was not seen in a sub-analysis restricted to the 11 randomized, controlled trials included in the meta-analysis. Several other trials showed that ACE inhibitors clearly reduce albuminuria in both type I and type II diabetes mellitus, irrespective of blood pressure level, with consistent antiproteinuric effects.[12,18–29] Although evidence from these studies has been interpreted as clearly demonstrating the beneficial renal effects of ACE inhibitors, there have been dissenting opinions[30–37] and calls for definitive long-term clinical trials to provide proof for the postulated effects.[38] One of the central issues in interpreting these and other studies on this issue revolves around the choice of outcome. Although it is generally recognized that outcomes employed in definitive studies need to be of direct clinical relevance,[39] such as mortality and morbidity, only five such studies have been conducted to date. The only study that did show a benefit for ACE inhibitors on renal disease in type I diabetes patients was based on patients with already evident diabetic nephropathy whose serum creatinine exceeded 1.5 mg/dl at study entry and only 3 years of follow-up.[12] In type II diabetes, on the other hand, the United Kingdom Prospective Diabetes study showed that patients who were given an ACE inhibitor had similar rates of renal failure than patients on a beta-blocker (rate ratio 0.91), after more than 8 years follow-up.[13] This study, however, had very low power to detect pragmatic differences, with only eight cases of renal failure in both groups combined. Moreover, the recent MICRO-Heart Outcomes Prevention Evaluation study found no reduction in the rate of progression to dialysis (rate ratio 1.22) in patients primarily with type II diabetes given an ACE inhibitor, albeit only after 2.5 years of follow-up.[14] The two most recent randomized trials of angiotensin-II-receptor blockers in type II diabetes patients with pre-existing kidney disease found slightly lower rates of ESRD relative to placebo over 4 years (rate ratios 0.83 and 0.72).[15,16] Thus, our finding of ACE inhibitors being associated with no decrease in the risk of renal failure compared with other antihypertensive agents over the long term in this largely type II diabetic cohort is consistent with these studies that either found no effect in the long term or a small beneficial effect during the first 3 to 4 years, but did not follow-up thereafter.

The finding of an elevated risk may have at least two possible explanations. First, it could be that ACE inhibitors prolong life, thus increasing the opportunity for ESRD incidence. Alternatively, ACE inhibitors, while apparently providing an early benefit to the kidney, could in fact damage the kidney in the longer term by mechanisms still unknown. Such a possibility needs to be studied in longer-term animal and possibly human studies. If such a mechanism exists, it is one of many potential explanations for the exponential rise in ESRD owing to diabetes over the past two decades.[10]

Our study design has strengths and limitations. Although a randomized trial would have been the preferred design, it would be expensive, lengthy, given the need to recruit large numbers and the extended follow-up, and may in fact not even be feasible. Indeed, we can anticipate that there may be difficulties in recruiting large numbers of patients with diabetes in such a trial, as their treating physicians may be reluctant to deprive them of the antiatherosclerotic effect of ACE inhibitors for over 10 years. Thus, our cohort study was designed specifically to emulate a randomized trial and to avoid confounding by indication, which arises from non-comparability of groups owing to selective prescribing and tends to bias the results of non-experimental studies of intended effects.[40] This was achieved by selecting the period of cohort entry to be between 1982 and 1986, as ACE inhibitors were first introduced in Saskatchewan in 1982 and clinical recommendations regarding the beneficial renal effects of ACE inhibitors came only after 1986. Indeed, animal experiments suggesting that ACE inhibitors were superior to other antihypertensive drugs in retarding the progression of renal disease were first reported in 1986,[41] and it was only several years later that ACE inhibitors were recommended for clinical use in diabetic patients.[42] Thus, direct confounding by indication for renal disease was likely absent from the cohort.

On the other hand, indirect confounding could have been present from the indication of ACE inhibitors for patients with congestive heart failure. The first trial showing the benefit of ACE inhibitors in congestive heart failure was published in 1987,[43] and some physicians may have already been using them between 1982 and 1986, which could have biased our study. This factor is an important potential confounding factor as it was also associated with an increased risk of end-stage renal failure in our study (rate ratio 2.9). We therefore controlled for this diagnosis in our analyses, both pre-existing before cohort entry or if it developed during follow-up. In stratifying for this diagnosis, we found that the rate ratio associated with ACE-inhibitor use was similar in patients with and without heart failure. The results, that still show an increased risk of end-stage renal failure in users of ACE inhibitors, decrease the likelihood, but do not eliminate the possibility of residual confounding by indication. Another aspect of confounding by indication is that calcium antagonists, which were also introduced in Saskatchewan in the early 1980s and could have thus been subject to similar selective prescribing, did not show an elevated rate ratio. Finally, the outcome we used, namely end-stage renal failure requiring dialysis treatment, has a low chance of misclassification and thus could not have biased the results in any

important way. Moreover, the fact that the rate ratios were consistent across subgroups of patients, such as the type of diabetes, the duration of hypertension, and the use of ACE inhibitors alone or in combination, substantiates the findings of this study.

This study indicates that the use of ACE inhibitors by patients with diabetes does not appear to decrease the long-term risk of ESRD. These data, in fact, suggest that this risk may be increased with ACE inhibitors. Whether clinicians should reconsider using these drugs in patients with diabetes to prevent kidney disease is unclear. Indeed, these drugs have been shown to be highly effective, compared with placebo, at preventing cardiovascular outcomes in this population. On the other hand, long-term studies have shown that they are just as effective as beta-blockers and that the focus of treatment should be on tight blood pressure control. More long-term studies of these major outcomes are needed to justify the extensive use of these drugs for renal protection in patients with diabetes.

MATERIALS AND METHODS

We used a population-based historical cohort study design, specifically devised to emulate a randomized, controlled trial.

Sources of data

The computerized databases of Saskatchewan Health, developed as a result of the universal health insurance program provided to residents of this Canadian province since 1975, formed the primary source of data for this study. All Saskatchewan residents (over 1 million) with a valid Health Services Card are eligible for coverage, with the exception of registered Indians and members of the Armed Forces, who in total represent less than 5% of the population. The databases contain identification and demographic details of all residents eligible for health services in Saskatchewan, as well as the date of death or the date of termination of coverage if the subject moved out of the Province. The prescription drugs' database contains data on outpatient prescription drug use, including the identity of the drug, its strength, and dosage form, as well as the date and quantity dispensed. The hospital data file contains data on all hospitalizations in Saskatchewan and includes information on primary and secondary discharge diagnoses, date of discharge, length of stay, and vital status at separation. The physician services database contains information on diagnosis and services rendered. These databases have been used extensively to study the effects of several prescription drugs at the population level.[44,45]

Cohort definition

All dispensed prescriptions for insulin and oral hypoglycemic agents were first used to identify the source population of diabetic subjects in Saskatchewan treated between the years 1976 and 1986. From this population, we formed the cohort of all subjects who were dispensed, during the period 1982 to 1986, the following antihypertensive medications: ACE inhibitors, beta-blockers, calcium channel blockers, thiazide diuretics, loop diuretics, and other agents, primarily consisting of methyldopa and hydralazine. The period for cohort entry was selected to start in 1982 as this is the year that ACE inhibitors were introduced in Saskatchewan. Cohort entry continued until December 31, 1986, so that subjects who received their first antihypertensive prescription after this date could not be enrolled as members of the cohort. This specific cohort closing date of December 1986 was chosen to ensure that confounding by indication does not bias the assessment of effectiveness, as the potential beneficial renal effects of ACE inhibitors only started to be discovered at that time[41] and clinical recommendations about this specific use only came much later.[42]

For subjects who initiated antihypertensive therapy between 1982 and 1986, time zero into the cohort was taken to be the date the first antihypertensive drug was dispensed. For subjects who initiated antihypertensive therapy before 1982, the definition of time zero depended on the antihypertensive agent. If those subjects had switched from any agent, primarily diuretics or beta-blockers, to either an ACE inhibitor or a calcium channel blocker between 1982 and 1986, the date of dispensing of the latter two was taken to be time zero. In subjects who used solely other agents between 1982 and 1986, time zero was taken to be a randomly selected dispensing date during this accrual period. Subjects were excluded if they had been hospitalized during the 2 years before cohort entry for acute renal failure, end-stage renal failure, renal transplantation, nephritis, nephropathy, nephrotic syndrome, unspecified renal failure, disorders resulting from impaired renal function and small kidney of unknown cause, or had received a treatment of dialysis.

All subjects were followed up until the date of coverage termination, of death, of the renal outcome under study, or December 1997, whichever occurred first. All prescriptions for antihypertensive drugs, other cardiovascular drugs, antidiabetic drugs dispensed throughout the follow-up, as well as all hospitalizations occurring during this period, were obtained.

Outcome

The outcome under study was end-stage renal failure requiring dialysis. Outcome data were obtained through the hospitalization and physician services databases. Chronic dialysis treatment was identified from a combination of the service dates for all dialysis treatments rendered and hospitalizations for end-stage renal failure requiring dialysis (ICD-9 code V56). The outcome was defined as requiring dialysis treatment of at least 6 weeks duration. Subjects with a duration of less than 6 weeks of dialysis, but who died within this treatment period, were also considered as cases if there were no indication that their renal failure was acute. The timing of the outcome was taken to be the first course of chronic dialysis.

Analysis

The study was designed to emulate a clinical trial with treatment allocation occurring at cohort entry. The primary analysis was thus an intention-to-treat analysis, based on the antihypertensive drugs dispensed at cohort entry. Owing to the large size of the cohort and the time-dependent nature of some covariates, a nested case–control approach to analysis was employed as an equivalent alternative to the proportional hazards model with time-dependent factors.[46] For each case of renal failure identified during follow-up, the risk set for this analysis was formed with all cohort members with a duration of follow-up as long or longer than the case's. The case's date of dialysis initiation was taken to be the index date for the case and the members of each risk set. Within each of these risk sets, we selected all controls who could be matched to the case on the type of diabetes treatment (insulin only, oral hypoglycemics only, combined therapy) before the index date, the duration of diabetes at the index date, as well as age within 5 years. The calculation of diabetes duration was incomplete for some subjects as data on treatment were only available as of 1976. Thus, the duration of diabetes was censored for

subjects who already had diabetes in 1976. Accordingly, the product-limit method was used to estimate the median duration of diabetes.

The rate ratio of renal failure associated with ACE-inhibitor use was estimated using conditional logistic regression, accounting for the matched nature of the risk sets. The primary measure of exposure at cohort entry was taken from the antihypertensive drugs dispensed during the first 90 days of follow-up after cohort entry. As subjects could have received more than one type of antihypertensive drug during this period, the regression analysis provided the independent effect of each antihypertensive drug type on the risk. The choice of 90 days was intended to be sufficiently short to avoid confounding by indication and long enough to capture other antihypertensive drugs given around the time of cohort entry, but not on that exact day. To compare the short- and long-term effects of ACE inhibitors, we repeated the analysis after stratification by more or less than 3 years of follow-up, the typical period employed in short-term trials.[12,14]

In addition to the matching factors, namely age within 5 years, type, and duration of diabetes, several potential confounding factors were used to adjust the estimated rate ratios. Besides sex, continuous age was used to account for residual confounding from the 10-year matching age categories. The year of cohort entry, from 1982 to 1986, was used to control for secular trends in antihypertensive drug use, whereas the use of antihypertensive drugs before cohort entry was used to control for prior hypertension. Cardiovascular disease and congestive heart failure, before cohort entry as well as during follow-up, were also used as covariates. Cardiovascular disease included hospitalizations for myocardial infarction, angina, and other acute and chronic ischemic heart disease, as well as prescriptions of nitrates. Congestive heart failure was defined by a hospitalization or by the dispensing of digoxin. The study had 80% power to detect the *a priori* hypothesized 40% reduction in the rate of the renal failure secondary to ACE-inhibitor use.

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